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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PONNALURI, PADMASHRI	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,696	SEM, DANIEL S.	
	Examiner	Art Unit	
	Padmashri Ponnaluri	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-51 and 57-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-51 and 57-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment and response filed on 2/10/05 has been fully considered and entered into the application.

2. Claims 52-56 have been canceled and new claims 60-70 have been added by the amendment filed on 2/10/05.

3. Claims 44-51, and 66-70 are currently pending and are being examined in this application.

4. This application is a divisional of Application NO. 09/083,537. The amendment to the specification to enter the priority application has been entered.

6. The objection to claims 52, 57 has been withdrawn in view of cancellation of claim 52.

7. The new matter rejection of claims 44-59 has been withdrawn in view of the amendment to the claims.

8. The rejection of claims 44-59 under 35 USC. 112, second paragraph for the reasons set forth in the previous office action has been withdrawn in view of the amendments.

9. The written description rejection of claims 44-51 has been maintained for the reasons of record set forth in the previous office action mailed on 8/10/04.

10. The enablement rejection of claims 44-51 has been maintained for the reasons of record set forth in the previous office action mailed on 8/10/04.

11. The lack of utility rejection of claims 44-51 has been maintained for the reasons of record set forth in the previous office action mailed on 8/10/04.

12. The obviousness-type double patenting rejection of claims 44-59 over co-pending application 10/103,535 have been maintained for the reasons of record set forth in the previous office action mailed on 8/10/04.

New Claim Objections/Rejections Necessitated by the Amendments

13. Claims 57 and 68 are objected to because of the following informalities: claims 57 and 68 are duplicate claims, and the scope of the claims is exactly same. Applicants are requested to either cancel the claim(s) or amend the claims.

14. Claims 58 and 69 are objected to because of the following informalities: claims 58 and 69 are duplicate claims, and the scope of the claims is exactly same. Applicants are requested to either cancel the claim(s) or amend the claims.

15. Claims 59 and 70 are objected to because of the following informalities: claims 59 and 70 are duplicate claims, and the scope of the claims is exactly same. Applicants are requested to either cancel the claim(s) or amend the claims.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 44-51, 57-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description Rejection.

The instant claims briefly recite a method for identifying a population of bi-ligands to dehydrogenase in a dehydrogenase family, comprising :

a) attaching a linker to a common ligand, wherein the common ligand is a cofactor or a analog thereof (claim 44), and the linker has sufficient length and orientation to direct a second ligand to a substrate binding site of dehydrogenase to form a module;

b) generating a population of bi-ligands comprising a second ligand and the module;

c) screening said population of bi-ligands for binding to a first dehydrogenase in said dehydrogenase family;

d) identifying a bi-ligand that binds to and has specificity to said first dehydrogenase;

e) screening said population of bi-ligands for binding to a second dehydrogenase in said dehydrogenase family; and

f) identifying a bi-ligand that binds to has a specificity for a second dehydrogenase in said dehydrogenase family.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The instant claims are directed to identifying "population of bi-ligands". The claims use generic terminology such as "common ligand", "receptor family" and "expansion linker". These terms are defined in the instant disclosure but the definitions are very broad.

The specification discloses that the 'common ligand' is a ligand that binds to a conserved site in a receptor family; 'specificity ligand' refers to a ligand when attached to a common ligand

binds to a specificity site on a receptor that is proximal to the conserved site; and 'expansion linker' is a chemical group that is capable of linking two ligands.

The specification discloses that receptor family is identified based on conserved and recognizable motif and in public databases. The specification lists the known common ligands to a certain receptor families. The specification further discloses methods for selecting common ligands and the use of NMR in determining the common ligand and determining the orientation which are useful in designing or synthesizing the bi-ligands. The specification has not disclosed the common ligands identified by the method or any analogs of the common ligand used in the synthesis of bi-ligands.

The specification discloses that a common ligand to a receptor family is already known (i.e., NAD and NADP). However, natural common ligands such as co-enzymes and co-factors described above and known derivatives of thereof often have limitations regarding their usefulness as a starting compound (see 0066). The position on a natural common ligand that is oriented towards specificity site is not always readily derivitizable for attaching a chemical group. Finally, some substrates or cofactors are highly charged, often making them less able to cross the membrane to target receptor inside the cell. Therefore, it is often desirable to identify additional common ligands that are useful for generating bi-ligands (see 0067).

The specification discloses methods for screening and/or NMR experiments to confirm the common ligand-expansion linker (module) binds to the conserved site in correct orientation. Once a common ligand-expansion linker has been identified that binds to the conserved site in correct orientation for attaching a specificity ligand to the expansion linker, a population of bi-ligands are generated, which are screened for binding to a target receptor. The specification

discloses that the method is useful in screening for high affinity, high specificity ligands to a target receptor. Thus, the bi-ligands of the claimed method are useful in further screening for a target or to identify the ligands.

The specification discloses that an expansion linker that provides an optimized orientation for attaching the specificity ligand is determined by further screening or experimentations.

The specification has not disclosed the analogs of the common ligands; the expansion linker and/or attachment site to the common ligand such that a second ligand binds to the linker, and the bi-ligands identified by the claimed method.

No specific structure of the identified "bi-ligand" is set forth and no specific "method for identifying a bi-ligand" is described in the instant disclosure. The specification has not taught the structure of the common ligand, and a second ligand linked through a linker (bi-ligand), that binds to two different dehydrogenases in the same family. Note that the recitation of dehydrogenase enzyme and the NAD or NADP as cofactors does not sufficiently teach the claimed invention. The structure of the claimed bi-ligands cannot be determined by the dehydrogenase enzyme or the cofactors. The specification discloses once a common ligand to a receptor in the enzyme family is determined, an expansion linker is attached to the common ligand. And once a common ligand-expansion linker has been identified that binds to the conserved site in the correct orientation for attaching a specificity ligand to the expansion linker, a population of bi-ligands is generated by attaching potential specificity ligands to the expansion linker that orients the specificity ligand to the specificity site. Thus, according to the specification disclosure initially a common ligand has to be determined which would be

useful in generating the bi-ligands of the instant invention, and then a proper linker has to be attached to the common ligand such that a potential specificity ligand can be attached to the common ligand-expansion linker. The specification has not disclosed the common ligands (other than NAD and NADP which are cofactors to dehydrogenase enzyme), which may be used in the claimed invention, and the expansion linker, which orients the specificity ligand to the specificity site, and the specificity ligand (or the second ligand).

And further the bi-ligands identified from the screening of binding to the first dehydrogenase, are further screened for bi-ligand that binds to and has specificity for a second dehydrogenase in the dehydrogenase family. Thus, further experimentation is required. The specification has not taught whether the first dehydrogenase and the second dehydrogenase are present on the same cell or how would the bi-ligand interacts with two different enzymes in the same family or the how the linker is linked such that the ligands can interact with two enzymes.

The exemplary figures of the instant specification do not show the structure of the bi-ligands interacting with two different enzymes in the same family. The present application fails to describe a specific example of identifying even a single compound, which is within the scope of the presently claimed invention. Applicant's claimed scope represents only an invitation to experiment regarding possible identified "bi-ligands" within the scope of the claims.

The specification discloses no examples of the preparation and use of such "bi-ligands". These compounds (i.e. "common ligand" and "specificity ligand") could encompass very different moieties such as peptides and organic molecules. Additionally, the description of "conserved site" as residues that are sufficient for activity (see 0030) and "specificity site" as a

binding site for a ligand exhibiting specificity for a receptor (see 0034) are simply not adequate support to show possession of the claimed invention.

With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires representative examples, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

The disclosure is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members, which are yet to be prepared or envisioned. This further evidences that instant disclosure does not constitute support for the claimed genus or a substantial portion thereof.

An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)(see MPEP 2163).

The instant specification does not disclose the structure of the common ligand linked via a linker to a second ligand (bi-ligand), which binds to a first dehydrogenase in the dehydrogenase family and further screening thus identified bi-ligands for binding to a second dehydrogenase in the same dehydrogenase family. The specification only discloses that nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide (NADP) are the cofactors of the dehydrogenase enzyme. However, the specification further discloses that the known cofactors have limitations regarding their usefulness as a starting compound, therefore, it is often desirable to identify additional common ligands that are useful for generating bi-ligands (see 0067). The specification has not disclosed whether NAD and NADP are useful as starting compounds in bi-ligand synthesis, or the cofactors NAD or NADP are modified such that they are useful as common ligands in the bi-ligands of the instant invention. Further the specification has not disclosed the cofactor analogs (common ligand) (the starting compound) which bind to either the first dehydrogenase or the second dehydrogenase in the dehydrogenase of the same family, and use of such compound in preparation of bi-ligands which bind to two dehydrogenases in the same family.

Thus, for the reasons set forth the claimed invention does not sufficiently teach the claimed method.

18. Claims 44-51, 57-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims briefly recite a method for identifying a population of bi-ligands to

dehydrogenase in a dehydrogenase family, comprising :

a) attaching a linker to a common ligand, wherein the common ligand is a cofactor or a analog thereof (claim 44), and the linker has sufficient length and orientation to direct a second ligand to a substrate binding site of dehydrogenase to form a module;

b) generating a population of bi-ligands comprising a second ligand and the module;

c) screening said population of bi-ligands for binding to a first dehydrogenase in said dehydrogenase family;

d) identifying a bi-ligand that binds to and has specificity to said first dehydrogenase;

e) screening said population of bi-ligands for binding to a second dehydrogenase in said dehydrogenase family; and

f) identifying a bi-ligand that binds to has a specificity for a second dehydrogenase in said dehydrogenase family.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims and the nature of the invention: The claims are drawn to a "method for identifying a bi- ligand to dehydrogenase" wherein the "bi-ligand" is made up of three parts: a "common ligand", a "second ligand" and "a linker." No limitations on the specific structure of the common ligand, specificity linker, a second ligand and further the identified "bi-ligand" are given and, as such, this could read on a wide variety of structures. The invention is such that each of the components must be present in operable form for successful practice of the invention. For example, the "common ligand" and "second ligand" must bind to their respective sites on the receptor and the sites must be able to be determined. And the specification discloses that the expansion linker has to orient the specificity ligand (or the second ligand) the specificity site. Thus, the three components in the bi-ligand are to be positioned or linked such a way that the bi-ligand can be bind to both the conserved site and the specificity site in the enzyme.

The state of the prior art and the level of predictability in the art: Compounds that interact with various enzyme targets were known in the art at the time of filing; however, only limited numbers of such compounds were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of *any* such compound. The specification discloses (by a general disclosure) that nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide (NADP) are the cofactors to dehydrogenase enzyme. The instant claim recites that the common ligand is cofactors to dehydrogenases. The specification discloses that even the natural common ligands such as co-enzymes and co-factors described above and known derivatives of thereof often have limitations regarding their usefulness as a starting compound (see 0066). The position on a natural common ligand that is oriented towards specificity site is not always readily derivitizable for attaching a chemical group. Finally, some

substrates or cofactors are highly charged, often making them less able to cross the membrane to target receptor inside the cell. Therefore, it is often desirable to identify additional common ligands that are useful for generating bi-ligands (see 0067). And further the specification has not disclosed whether the NAD and NADP are modified such that they would be useful in generating the bi-ligands. The specification has not disclosed the structure of the common ligand (NAD or NADP) linked via linker to a second ligand, such that the bi-ligands bind to two different sites on the same enzyme, and the bi-ligands are capable of binding to two different enzymes in the same family.

Further, the identified "bi-ligands" of the instant claims require "common ligands" and "second ligand" (specificity ligand), and the specification discloses only NAD and NADP as the common ligands to the dehydrogenases, and has not even disclosed the second ligands (specificity) which can be used in generating the bi-ligands. And further the instant claim recites that the bi-lgands, which are identified having specificity to dehydrogenase are used in further screening for a bi-ligand that binds to and has specificity to a second dehydrogenase in dehydrogenase family. It is not well known in the art to link two ligands, which will bind to different sites on the enzyme. The bi-ligand of the instant claim has the following three components, 1) a common ligand binds to the conserved site on the receptor, 2) the specificity ligand binds to the specificity site proximal to the conserved site, and 3) the linker linking the common ligand and the specificity ligand, such that the bi-ligand binds to two different binding sites on the enzyme. And further, it is not clear how the bi-ligands identified as binding one dehydrogenase in the family bind to a different dehydrogenase in the same family. The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict

their structures of the common ligand analogs . Moreover, the claims require the presence of a "common ligand" which is a "cofactor " or is a "**cofactor analog**" and additional ligand (second ligand or specificity ligand) that bind to "substrate binding sites" of a first and a second enzyme in an "enzyme family". One of ordinary skill would not know, *a priori*, how to determine the structure of such ligands because the determination of the different binding sites in an "enzyme family" would be unpredictable. Applicant's claimed scope of compounds represents only an invitation to experiment regarding possible methods of identification of undefined "bi-ligands" (see also above rejection concerning written description and cases cited therein). The length or the compound structure of the expansion linker, which links the common ligand and the specificity ligand is not known, and further the expansion linker has to bind to the second ligand (specificity ligand) in such a way that the specificity ligand (second ligand) binds to the specificity site on the receptor and the common ligand binds to the conserved site of the receptor. Note that the recitation of dehydrogenase enzyme and the NAD or NADP as cofactors does not sufficiently teach the claimed invention. The specification has not taught bi-ligands comprising NAD or NADP linked via an expansion linker to the specificity ligand, and such bi-ligands bind to both the conserved site and specificity site of the receptor (enzyme). Further the specification has not disclosed the length or the orientation of the linker such that second ligand (specificity ligand) is positioned such that the second ligand binds the specificity site on the receptor.

The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

The existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure: Applicants have provided **no** working examples and the state of the prior art is such that one of ordinary skill could not predict how to determine and then link the various moieties that make up the identified "bi-ligand" as required by the instant claims. Therefore, further research would be necessary to make or use the invention and it would require undue experimentation to carry out the invention as claimed. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the invention would require undue experimentation.

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

20. Claims 44-51, 57-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44-51, 57-70 are vague and indefinite. The claimed method step c) recites screening a population of bi-ligands for binding to a first dehydrogenase, and step d) recites identifying a bi-ligand that binds to has specificity to said first dehydrogenase, and step e) recites screening said population of bi-ligands for binding to a first dehydrogenase . The claimed can be

interpreted as several ways. It is not clear whether applicants mean that the identified bi-ligands of the instant method bind to more than one dehydrogenase in the same family at the same time (i.e., bi-target) or the bi-ligands which has specificity to a first dehydrogenase also has specificity to a second dehydrogenase family, or does applicants mean that the population or the library of bi-ligands in which one component is varied (either common ligand, linker or the second ligand) and other components (i.e., common ligand, linker or the second linker) are kept constant, such that the bi-ligands in the library would bind to conserved site in the dehydrogenase family and have a different second ligand which would be specific to that particular dehydrogenase. The bi-ligand of the instant claim has the following three components, 1) a common ligand binds to the conserved site on the receptor, 2) the specificity ligand binds to the specificity site proximal to the conserved site, and 3) the linker linking the common ligand and the specificity ligand, thus it is not clear how the bi-ligands of the instant claims bind to and has specificity to a second dehydrogenase in dehydrogenase family.

Claims 44-51, 57-70 recite the limitations such as "said bi-ligand", "said expansion linker" which have insufficient antecedent basis for these limitations in the claim. Applicants are requested to amend the claims.

21. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

22. Claims 44-51, 57-70 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

The instant claims briefly recite a method for identifying a population of bi-ligands to dehydrogenase in a dehydrogenase family, comprising :

a) attaching a linker to a common ligand, wherein the common ligand is a cofactor or a analog thereof (claim 44), and the linker has sufficient length and orientation to direct a second ligand to a substrate binding site of dehydrogenase to form a module;

b) generating a population of bi-ligands comprising a second ligand and the module;

c) screening said population of bi-ligands for binding to a first dehydrogenase in said dehydrogenase family;

d) identifying a bi-ligand that binds to and has specificity to said first dehydrogenase;

e) screening said population of bi-ligands for binding to a second dehydrogenase in said dehydrogenase family; and

f) identifying a bi-ligand that binds to have specificity for a second dehydrogenase in said dehydrogenase family.

According to the text of 35 USC sec. 101, an invention must be useful. Our reviewing courts have applied the labels, Aspecific utility (or A practical utility) to refer to this aspect of the A useful invention requirement of sec. 101. (Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980)). In Nelson, the court characterized Aspecific utility (or Apractical utility) as Aa shorthand way of attributing real-world value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner, which provides some immediate benefit to the public. (Id. at 856.)

Note that the recitation of dehydrogenase enzyme and the NAD or NADP as cofactors or common ligands do not impart any specific utility of the bi-ligands identified by the claimed

method. The structure of the bi-ligands cannot be determined by the dehydrogenase enzyme or the cofactors. The bi-ligand (common ligand, specificity ligand linked via an expansion linker) to dehydrogenase enzyme and the population of bi-ligands (common ligand – linker – specificity ligand) are not supported by a specific asserted utility and do not, without further research and experimentation, provide an immediate benefit to the public. Rather, the bi-ligand comprises compounds , which are yet to be tested for their therapeutic activity. For example, the instant specification, (page 12, 0103 on PG PUB US 2001/0006822 A1) discloses that the bi-ligand can be validated as a likely effective therapeutic agent (if the target receptor is a pathogenic organism, the bi-ligand can be tested for inhibitory activity in the target organism). Thus, the bi-ligands have to be further tested for activity. The specification has not disclosed the structure of the common ligand (NAD or NADP) linked via linker to a second ligand, such that the bi-ligands bind to two different sites on the same enzyme, and the bi-ligands are capable of binding to two different enzymes in the same family.

Thus, any benefit to the public (to one of ordinary skill in the art) is speculative. There is no basis in the specification upon which to conclude that *any* of the compounds encompassed by bi-target or the bi-ligand of the instant claims **are**, or will turn out to be, biologically active after testing. The specification further discloses that the use of NAD or NADP (cofactors) as common ligands. The specification has not disclosed whether the NAD and NADP are modified such that they would be useful in generating the bi-ligands. The specification has not disclosed the bi-ligands comprising NAD or NADP as common ligand, linked to a second ligand via an expansion linker would bind to specificity site and conserved site of dehydrogenase enzyme. The therapeutic use of the bi-target ligand is to take place at some future time, only when the

properties of the bi-ligands have been elucidated by the experimental methods (screening assays). Absent a disclosure of those properties, the asserted utility of therapeutic use lacks specificity.

Further the specification discloses that the common ligand-expansion linker (module) have to be screened to identify the common-ligand in that the linker is attached to the common ligand oriented towards the specificity site. The expansion linker that provides the optimized orientation for attaching a specificity ligand has to be identified. Thus, further experimentation in determining the common ligand, expansion linker is required.

The instant specification discloses that the bi-ligands (common ligand – linker – specificity ligand) act as therapeutic agents. A "specific utility" is specific to the subject matter claimed. This is contrast with a general utility that would be applicable to the broad class of invention. Indicating the compound may be useful in treating a disorder (bacterial infection) or has useful biological properties would not be sufficient to define specific utility of the compound (e.g., see MPEP 2107.01). Further the specification has not shown the correlation between the similar known compounds, which have established utility and/or data from in vivo or in vitro testing of the compounds to support the therapeutic utility.

Note, because the claimed invention is not supported by a specific asserted utility for the reasons just set forth, credibility cannot be assessed.

This is not to say that inventions that are to be used exclusively in a research setting (i.e., research tools) always lack a specific asserted utility. Indeed, many research tools such as telescopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility. (See USPTO Utility Guidelines, page 12.) However,

inventions that have a specifically identified utility must be distinguished from those whose utility requires further research to identify or reasonably confirm. (Id.) Research tools (such as gas chromatographs, screening assays, etc.) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result. The bi-ligands (common ligand – linker – specificity ligand) of the instant claims are not research tools in this sense. Rather, they are themselves the subject of basic research, whose usefulness or lack thereof has yet to be established. Merely labeling the instant libraries as Aresearch tools does not impart the specific utility required by this statute.

In the absence of an asserted specific utility, the useful requirement may be established by reference to a well-established utility. A well established utility is a Aspecific utility which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. The bi-ligands (common ligand – linker – specificity ligand) of the instant claims are not supported by a well-established utility, however, because neither the specification as filed nor any art of record discloses or suggests any property or activity for the compounds such that another non-asserted utility would be well established for the compounds. Further, the compounds of the instant claims are not recognizable as analogous to compounds with a recognized pharmacological (or other) activity. In the absence of any data as to their activity, there is no basis upon which to base either a specific or a well-established utility. NAD and NADP are known as cofactors of enzyme dehydrogenase, however it is not known that two ligands of which one is NAD or NADP and the other unknown ligand are linked via a linker such that the ligands bind to two

different sites on the dehydrogenase. Thus, a well-established utility to the bi-ligands of the instant claimed method cannot be determined.

Claims 44-51, 57-70 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Double Patenting

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. Claims 44-51, 57-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 10/103,535. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 13-28 of the reference are drawn to method of identifying bi-ligand to a receptor, which would read on the instant claims (receptor is a genus, and the dehydrogenase is a species), and the claim 1 method of identifying a common ligand is required to practice the claimed method. Thus, the reference claims clearly read on the instant claimed method.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

NOTE the assignee of the reference application is same as the instant application.

25. Claims 44-51, 57-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 10/672,859. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-23 of the reference are drawn to method of generating a library of bi-ligands, which are used in the instant claimed method. Thus, the reference libraries are required to practice the instant claimed method.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

NOTE the assignee of the reference application is same as the instant application.

Response to Arguments

26. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

27. Applicant's arguments with respect to claims 44-57, written description rejection and enablement rejection have been considered but are moot in view of the amendments and the new ground(s) of rejection.

NOTE that these rejection over claims 44-57 has been maintained for the reasons of record, and rewritten as a new rejection in view of the amendments to the claims. Further, from applicant's arguments it has been concluded that applicants seem to be interpreting that the 'lack of written description rejection' is only applicable to product claims, not to the method claims. Applicants interpretation is not proper, e.g., see Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)(see MPEP 2163).

In the instant claimed method, neither the starting compounds (common ligands, expansion linker, second ligand), nor the final compounds (bi-ligands) (how the tree components are linked or the structure) identified through various rounds of screening steps are known. According to the specification disclosure even if the common ligands (NAD or NADP common ligands) to enzymes in the dehydrogenase family are known, the position on a natural common ligand that is oriented towards specificity site is not always readily derivitizable for attaching a chemical group. And further, the specification discloses that some substrates or cofactors are highly charged, often making them less able to cross the membrane to target receptor inside the cell. Therefore, it is often desirable to identify additional common ligands that are useful for generating bi-ligands. Thus, the starting compounds (common ligands, expansion linkers and the

second ligands (specificity ligands)) are not known to generate the bi-ligands, which are screened in the instant claimed method. The specification disclosure is hypothetical and no working examples of bi-ligands generated and used in the claimed method are taught. Applicant's arguments regarding the analogs of NAD and NADP are well known have been considered and is not persuasive. Since the instant claims are not drawn to just the analogs of NAD or NADP, the instant claim bi-ligands require three components and proper linking of these components such that the bi-ligands simultaneously bind to both the conserved site and the specificity site of the dehydrogenase enzyme. The knowledge of analogs of the NAD or NADP is not sufficient to practice the claimed method. Thus, for the reasons set forth above the written description rejection of record has been maintained.

28. Applicant's arguments filed on 2/10/05, regarding the lack of utility rejection have been fully considered but they are not persuasive.

Applicants argue that the methods for generating a population of library of compounds that allow the same population or library to be screened against multiple targets, which bind a common ligand, has specific and substantial utility. Applicant's arguments have been considered and are not persuasive. The bi-ligands generated and are identified by the claimed method are not disclosed, and the specification has not disclosed the bi-ligands comprising common ligand, expansion linker and the second ligand (specificity ligand) bind to enzymes at two different sites, and also bind to multiple targets. The specification disclosure is an invitation to experiment, and the recitation of NAD and NADP as co-factors (common ligands) to dehydrogenase enzyme would not be considered as specific and substantial utility. The specification has not taught the final compounds "bi-ligands", which bind to multiple targets or bind to two different sites on a

enzyme, such that the asserted utility is considered as specific utility. The specification discloses hypothetical compounds prepared by the hypothetical methods. The specification has not shown that the bi-ligands identified from the claimed method have therapeutic utility.

Applicants further argue that 'the claimed method compounds can be screened for specific therapeutic applications' is considered as useful biological property. Applicant's arguments have been considered and are not persuasive.

According to MPEP Utility guidelines, *'indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.'*

A statement that a composition has an unspecified "biological activity" or that does not explain why a composition with that activity is believed to be useful fails to set forth a "specific and substantial utility." Brenner v. Lanson, 383 US 519, 148 USPQ 689 (1966); In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967) (indication that compound is "biologically active" or has "biological properties" insufficient standing alone).

On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved; (B) A method of treating an unspecified disease or condition;

(C) A method of assaying for or identifying a material that itself has no specific

and/or substantial utility (See MPEP 2107, under 'substantial Utility).

In the absence of teachings of final compounds or the structures of the compounds, screening for biologically active compounds is not considered as specific and substantial utility. Since the final compounds which are used in the claimed method are not generated, and the specification has not disclosed any of the biologically active final compounds (bi-ligands), such that the therapeutic utility is considered as specific utility.

And the identified final bi-ligands of the instant claimed method require further research, i.e., further experimentation required to determine the structure of the compounds, and further screening assays to determine the biological property or the therapeutic application. Because the inventions require further research or experimentation to determine the therapeutic utility, the invention lacks 'substantial utility.'

Thus, for the reasons of record set forth the lack of utility rejection has been maintained.

29. Applicant's arguments filed on 2/10/05, regarding the obviousness-type double patenting rejection over 10/103,535 have been fully considered but they are not persuasive. Applicant's request that the rejection be held in abeyance until there is indication of allowable subject matter, has been considered. However the rejection of record is maintained until the terminal disclaimer to over come has filed and considered in this application.

Conclusion

30. No claims are allowed.

31. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 271-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

PADMASHRI PONNALURI
PRIMARY EXAMINER

24 May 2005